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FILING DATE: *November 07, 2003*
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PROVISIONAL APPLICATION FOR PATENT
COVER SHEET

Case No. **ACADIA.040PR**
Date: November 7, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: PROVISIONAL PATENT APPLICATION

Sir:

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c).

For: **IDENTIFICATION OF COMPOUNDS WITH ACTIVITY ON LIPOXIN RECEPTORS**

Name of First Inventor: Norman Nash
Residence Address: San Diego, CA

Name of Second Inventor: Audra Scully
Residence Address: San Diego, CA

Enclosed are:

(X) Specification in 43 pages.

(X) A return prepaid postcard.

(X) The Commissioner is hereby authorized to charge the filing fee of $80 and any additional fees which may be required, now or in the future, to Account No. 11-1410.

Was this invention made by an agency of the United States Government or under a contract with an agency of the United States Government?

(X) No.

( ) Yes. The name of the U.S. Government agency and the Government contract number are:

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Attorney Docket No.	:	ACADIA.040PR
Applicant(s)	:	Nash, et al.
For	:	IDENTIFICATION OF COMPOUNDS WITH ACTIVITY ON LIPOXIN RECEPTORS
Attorney	:	Sam K. Tahmassebi
"Express Mail" Mailing Label No.	:	EV 325004806 US
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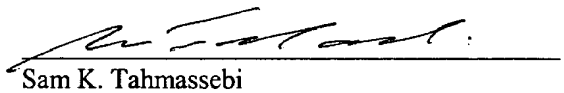

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Identification of Compounds with Activity on Lipoxin Receptors

Field of the Invention

[0001] Aspects of the invention described below relate to compounds affecting a response at receptors of the lipoxin family, and more specifically the FPRL1 receptor. Additionally, disclosed are the use of such compounds to alleviate symptoms of the immune response as a result of activation of neutrophils, leading to: vasoconstrictive, inflammatory, myeloid suppressive, cardiovascular, and gastrointestinal diseases.

Background of the Invention

[0002] The immune response in human is a complex cascade of events that can be triggered by both endogenous and exogenous stimuli and once triggered, if gone unchecked, can result in significant tissue damage and eventual death. A diverse range of endogenous mediators are involved in this response, with key roles being played by eicosanoids such as prostaglandins and leukotrienes. These molecules exert their actions through activation of receptors on various leukocyte populations including neutrophils. Neutrophils are within the first line of host defense and, by their ability to phagocytize microbes, can protect the host from infection. However, they can also give rise to vascular injury and contribute to increased vascular permeability, edema, and subsequent release of chemoattractants.

In an effort to balance the activation of neutrophils, humans and other organisms have developed a negative feedback loop that acts as a breaking signal. One of the major effectors of this phenomenon is the lipoxin receptor FPRL1.

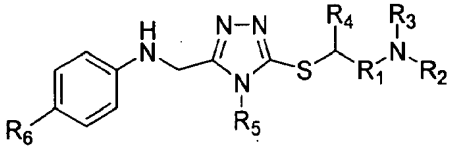
FPRL1 was first identified by Murphy et al. as a structurally related homologue of the N-formyl peptide receptor (FPR). This peptide, when released by bacteria during infection, had been shown to mediate chemotaxis and degranulation. Subsequent work with FPRL1 has shown that it acts as a receptor for the host-derived eicosanoid LXA4 and has its expression primarily on neutrophils and monocytes. Additionally, the hexapeptide WKYMVM has also been shown to act as an agonist of the FPRL1 receptor in experiments looking at chemotaxis as well as in vitro assays designed to measure calcium mobilization.

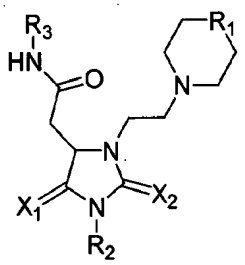
The action of agonism of the FPRL1 receptor by these agents results in a downregulation of proinflammatory chemokines and eventual cessation of the acute

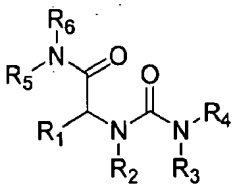
inflammatory response. The importance of this "stop signal" is highlighted by the observation that excessive acute inflammation caused by aberrant host recognition or prolonged activation of effector cells can result in an array of proinflammatory amplifying cellular responses that acutely can give rise to reperfusion injury and chronic inflammatory diseases like rheumatoid arthritis. Most of the eicosanoids derived from the metabolism of arachidonic acid have been demonstrated to exacerbate inflammation in such diseases as asthma, glomerulonephritis, rheumatoid arthritis and Alzheimer's disease. In contrast, the lipoxins have been shown to act as alleviators of inflammatory responses; thus highlighting the importance of developing small molecule FPRL1 agonists as anti-inflammatory therapeutics.

Summary of the Invention

Disclosed herein are compounds of Formula I, Formula II, or Formula III

(I) 

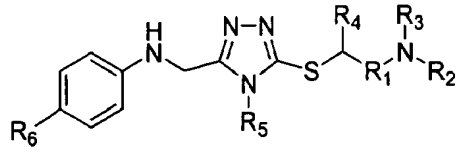
(II) 

(III) 

as defined herein, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, that selectively activate the FPRL1 receptor. Further disclosed are methods of alleviating inflammatory responses by regulating key steps in leukocyte trafficking and preventing neutrophil-mediated tissue damage by administering to a subject a therapeutically effective amount of a compound of Formula I, Formula II, or Formula III. In addition, methods of modulating, or specifically agonizing, the FPRL1 receptor administering an effective amount of a compound of Formula I, Formula II, or Formula III are also disclosed.

Detailed Description of the Preferred Embodiment

In a first aspect, disclosed herein is a compound of Formula I

(I) 

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

R_1 is selected from the group consisting of C_1-C_{10} straight chained or branched alkylene, oxygen, sulfur, NQ, CHCN, C=O, C=S, C=NQ, S=O, $S(=O)_2$, C=NOQ,

wherein Q is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl;

each of R_2, R_3, R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_2-C_{10} straight chained or branched alkenyl, C_2-C_{10} straight chained or branched alkynyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, -CN, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, and $-SR_7$,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched

alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl; or

R_3 and R_4 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound disclosed herein with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound disclosed herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

The term "ester" refers to a chemical moiety with formula -$(R)_n$-COOR', where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1.

An "amide" is a chemical moiety with formula -$(R)_n$-C(O)NHR' or -$(R)_n$-NHC(O)R', where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1. An amide may be an amino acid or a peptide molecule attached to a molecule of disclosed herein, thereby forming a prodrug.

Any amine, hydroxy, or carboxyl side chain on the compounds disclosed herein can be esterified or amidified. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as

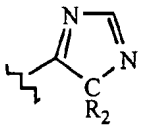
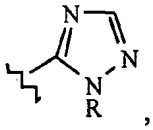
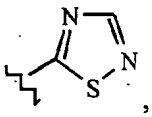
Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated by reference herein in its entirety.

A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound disclosed herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

The term "aromatic" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups. The term "carbocyclic" refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. The term "heteroaromatic" or "heteroaryl" refers to an aromatic group which contains at least one heterocyclic ring.

Examples of aryl ring include, but are not limited to, benzene, and substituted benzene, such as toluene, aniline, xylene, and the like, naphthalene and substituted naphthalene, and azulene.

Examples of heteroaryl ring include, but are not limited to, furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, thiadiazole, pyran, pyridine,

piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine,  ,  , and  , where R is as defined herein.

As used herein, the term "alkyl" refers to an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 5 carbon atoms. The alkyl group of the compounds disclosed herein may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to,

methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Wherever a substituent is described as being "optionally substituted" that substituent may be substituted with one of the above substituents.

The term "alkylene" refers to an alkyl group, as defined here, which is a biradical and is connected to two other moieties. Thus, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), proylene ($-CH_2CH_2CH_2-$), isopropylene ($-CH_2-CH(CH_3)-$), and isobutylene ($-CH_2-CH(CH_3)-CH_2-$) are examples, without limitation, of an alkylene group.

The substituent "R" appearing by itself and without a number designation refers to a substituent selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

An "O-carboxy" group refers to a $RC(=O)O-$ group, where R is as defined herein.

A "C-carboxy" group refers to a $-C(=O)OR$ groups where R is as defined herein.

An "acetyl" group refers to a $-C(=O)CH_3$, group.

A "trihalomethanesulfonyl" group refers to a $X_3CS(=O)_2-$ group where X is a halogen.

A "cyano" group refers to a -CN group.

An "isocyanato" group refers to a -NCO group.

A "thiocyanato" group refers to a -CNS group.

An "isothiocyanato" group refers to a -NCS group.

A "sulfinyl" group refers to a -S(=O)-R group, with R as defined herein.

A "S-sulfonamido" group refers to a $-S(=O)_2NR$, group, with R as defined herein.

A "N-sulfonamido" group refers to a $RS(=O)_2NH-$ group with R as defined herein.

A "trihalomethanesulfonamido" group refers to a $X_3CS(=O)_2NR-$ group with X and R as defined herein.

An "O-carbamyl" group refers to a $-OC(=O)-NR$, group-with R as defined herein.

An "N-carbamyl" group refers to a $ROC(=O)NH-$ group, with R as defined herein.

An "O-thiocarbamyl" group refers to a $-OC(=S)-NR$, group with R as defined herein.

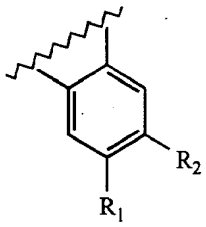
An "N-thiocarbamyl" group refers to an $ROC(=S)NH-$ group, with R as defined herein.

A "C-amido" group refers to a -C(=O)-NR_2 group with R as defined herein.

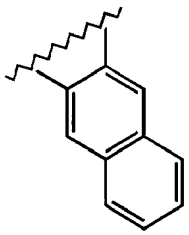
An "N-amido" group refers to a RC(=O)NH- group, with R as defined herein.

The term "perhaloalkyl" refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

When two substituents and the carbons to which they are attached form a ring, it is meant that the following structure:

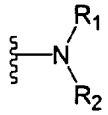


is representative of the following structure:



In the above example, R_1 and R_2 and the carbons to which they are attached form a six-membered aromatic ring.

When two substituents and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring; it is meant that the following structure:



is representative of, for example, the following structures:

Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substitutent is a group that may be substituted with one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heterocyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido,

S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

In certain embodiments, R_1 in the compound of Formula I is hydrogen or C_1-C_{10} straight chained alkyl. In some embodiments, R_1 is hydrogen or C_1-C_5 straight chained alkyl. In further embodiments, R_1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, and isopentyl.

In some embodiments, R_2 in the compound of Formula I is selected from the group consisting of hydrogen, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is hydrogen or C_1-C_{10} straight chained alkyl. In certain embodiments, R_2 is selected from the group consisting of hydrogen, hydroxy, nitro, halogen, and $-OR_7$, and wherein R_7 is hydrogen or C_1-C_3 straight chained alkyl. In other embodiments, R_2 is selected from the group consisting of hydrogen, hydroxy, nitro, chloro, bromo, methoxy, and ethoxy.

In certain embodiments, R_3 in the compound of Formula I is selected from the group consisting of hydrogen, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is hydrogen or C_1-C_{10} straight chained alkyl. In some embodiments, R_3 is selected from the group consisting of hydrogen, hydroxy, nitro, halogen, and $-OR_7$, and wherein R_7 is hydrogen or C_1-C_3 straight chained alkyl. In other embodiments, R_3 is selected from the group consisting of hydrogen, nitro, chloro, and iodo.

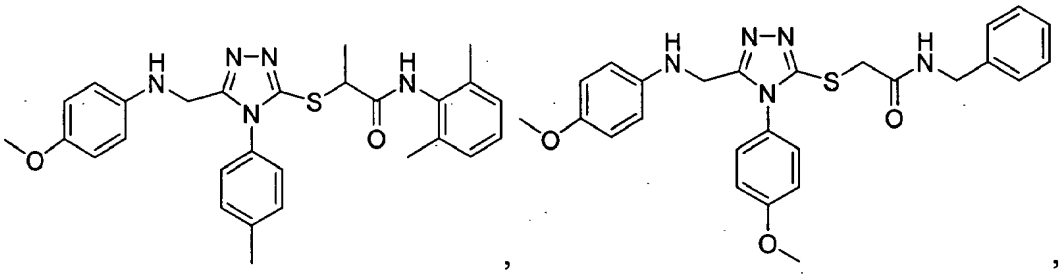
Embodiments include those in which R_4 in the compound of Formula I is selected from the group consisting of hydrogen, C_1-C_{10} straight chained alkyl, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein each R_7 is independently C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl. In some embodiments, R_4 is selected from the group consisting of hydrogen, C_1-C_3 straight chained alkyl, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein each R_7 is independently C_1-C_3 straight chained alkyl optionally substituted with an aryl. In yet other embodiments, R_4 is selected from the group consisting of hydrogen, methyl, ethyl, hydroxy, nitro, amino, chloro, fluoro, methoxy, ethoxy, methylamino, dimethylamino, diethylamino, and benzyloxy.

In further embodiments, R_5 in the compound of Formula I is selected from the group consisting of hydrogen, C_1-C_{10} straight chained alkyl, hydroxy, nitro, amino, halogen, perhaloalkyl, $-OR_7$, and $-N(R_7)_2$, and wherein each R_7 is independently C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl. In other embodiments, R_5 is selected from the group consisting of hydrogen, C_1-C_3 straight chained alkyl, hydroxy, nitro, amino, halogen, perhaloalkyl, $-OR_7$, and $-N(R_7)_2$, and wherein each R_7 is independently C_1-C_3 straight chained alkyl. In certain embodiments, R_5 is selected from the group consisting of hydrogen, hydroxy, chloro, bromo, trifluoromethyl, and methoxy.

In some embodiments R_6 is hydrogen.

As mentioned above, in some embodiments R_2 and R_3 and the nitrogen to which they are attached form a fused heteroaryl or heterocyclic alkyl ring. In some embodiments, the ring is a fused heterocyclic alkyl ring, which may be a N-morpholine or pyrrole.

In certain embodiments, the compound of Formula I is selected from the group consisting of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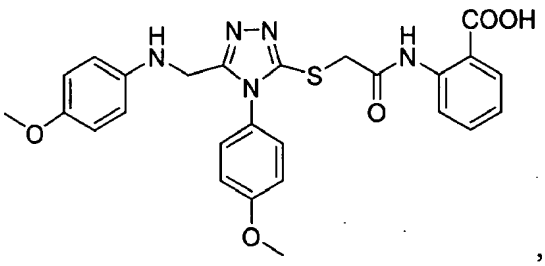
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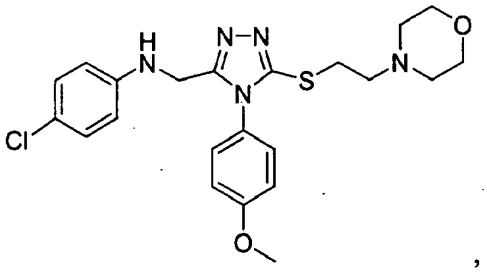
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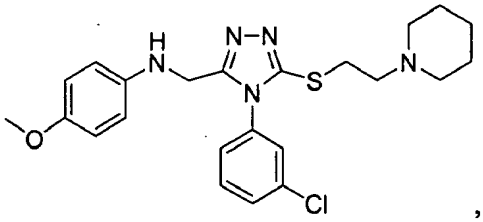
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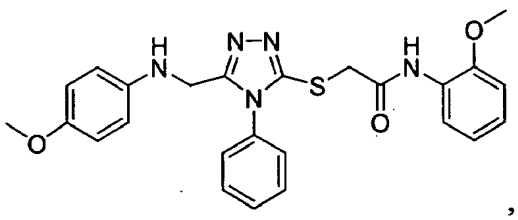
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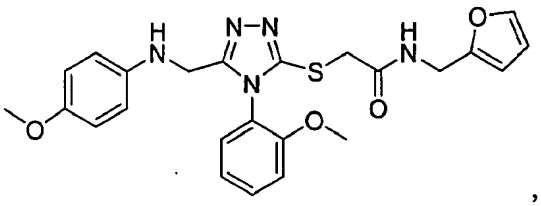
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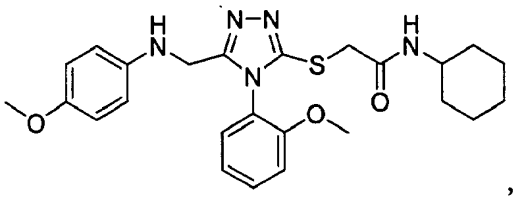
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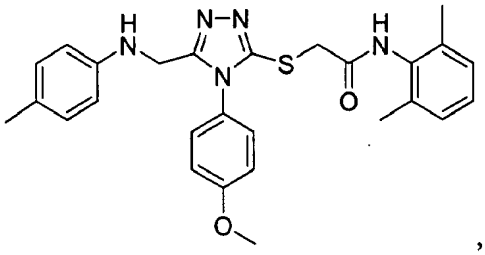
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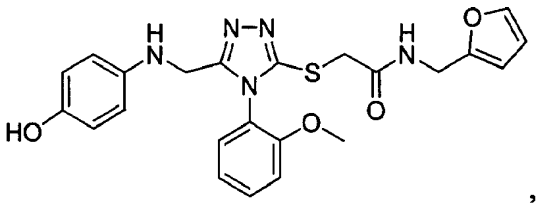
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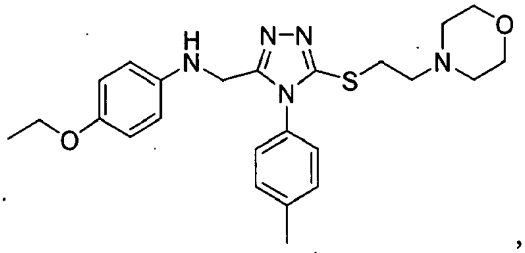
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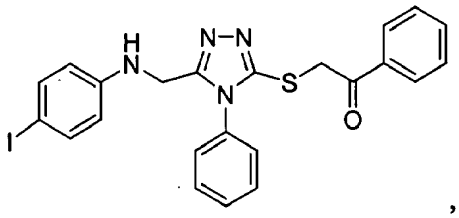
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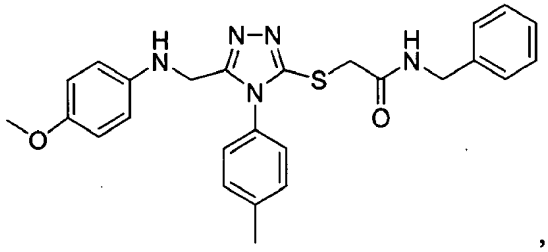
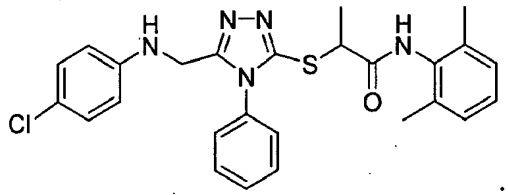
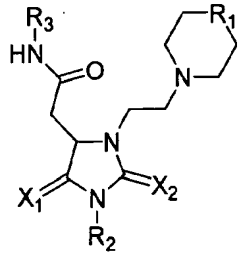


, and

In another aspect, disclosed herein is a compound of Formula II

(II)


or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

each of X_1 and X_2 is independently oxygen or sulfur;

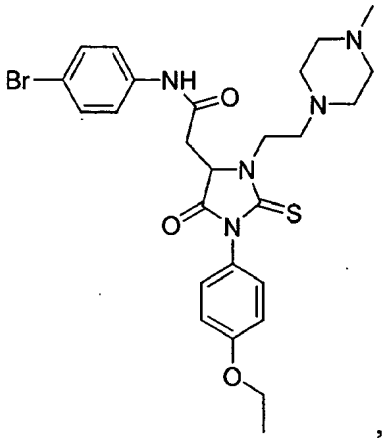
R_1 is selected from the group consisting of C_1-C_{10} straight chained or branched alkylene, oxygen, sulfur, NQ, CHCN, C=O, C=S, C=NQ, S=O, $S(=O)_2$, C=NOQ

wherein Q is selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl;

each of R_2, R_3, is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_2-C_{10} straight chained or branched alkenyl, C_2-C_{10} straight chained or branched alkynyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, -CN, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, , and $-SR_7$,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl.

In certain embodiments, the compound of Formula II is selected from the group consisting of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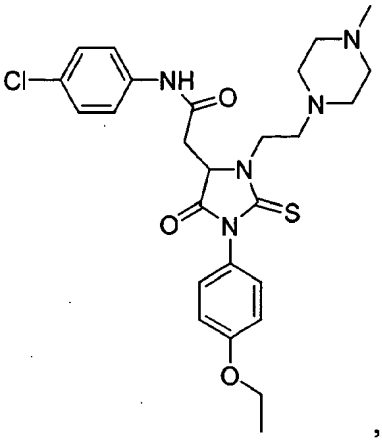
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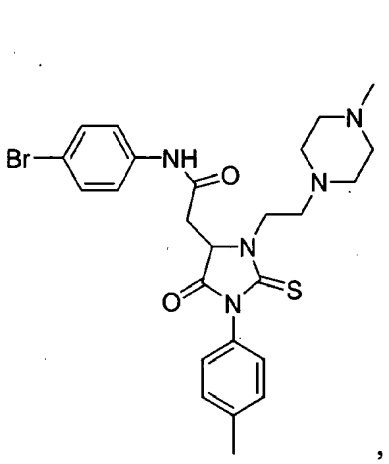
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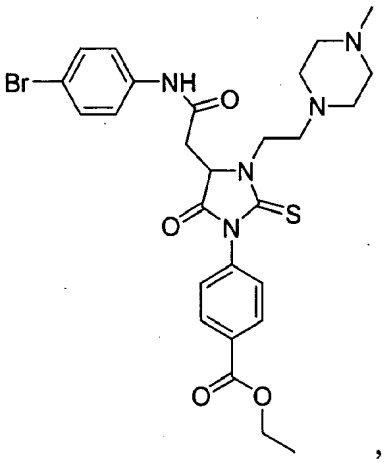
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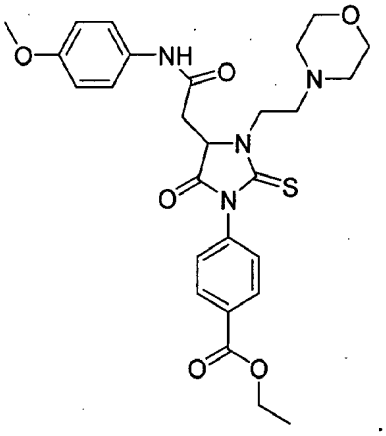
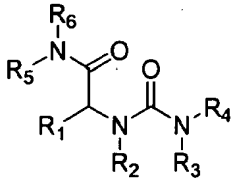


In yet another aspect, disclosed herein is a compound of Formula III

(III)


or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

each of R_1, R_2, R_3, R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_2-C_{10} straight chained or branched alkenyl, C_2-C_{10} straight chained or branched alkynyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, -CN, $-C(=Z)R_7$,$-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, , and $-SR_7$

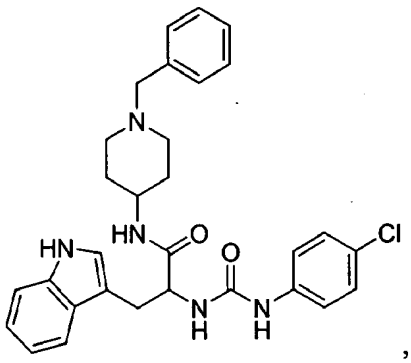
wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl; or

R_3 and R_4 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring;

R_4 and R_5 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring; or

R_1 and R_2 and the nitrogen to which R_2 is attached form a fused heteroaryl, or heterocyclic ring.

In certain embodiments, the compound of Formula III is selected from the group consisting of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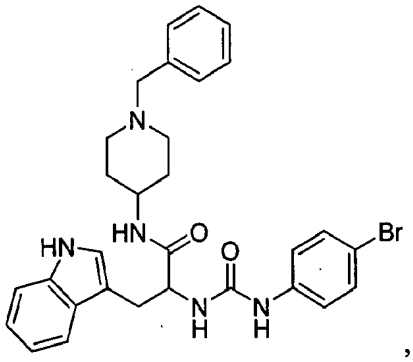
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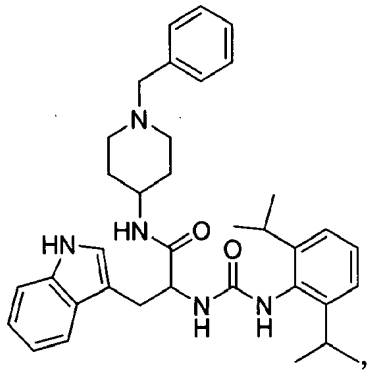
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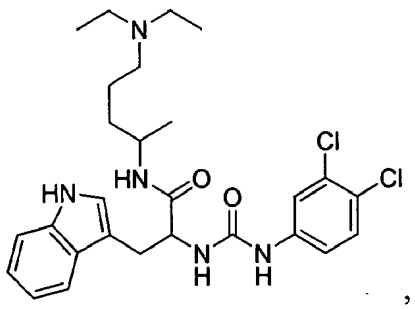
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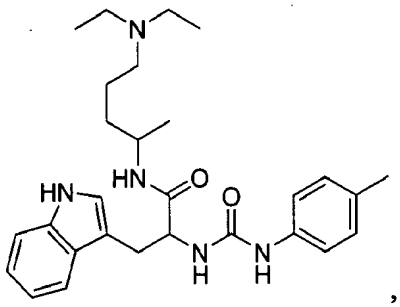
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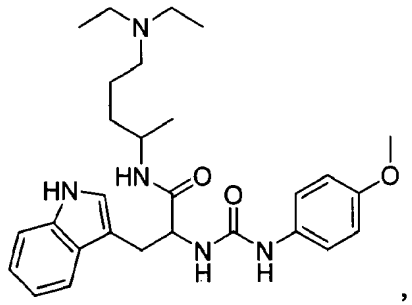
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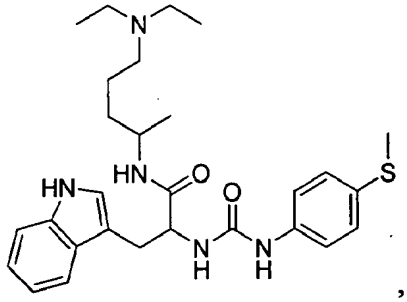
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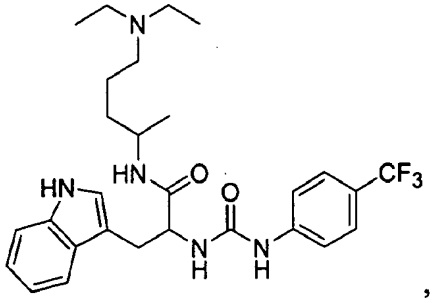
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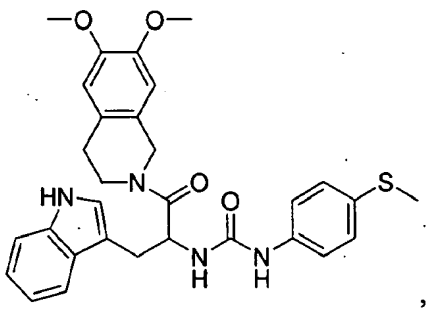
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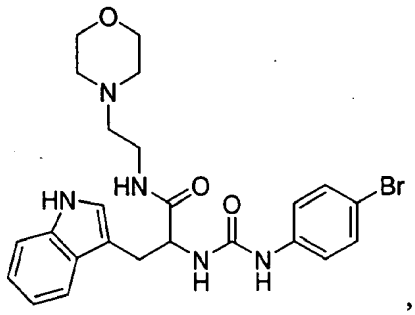
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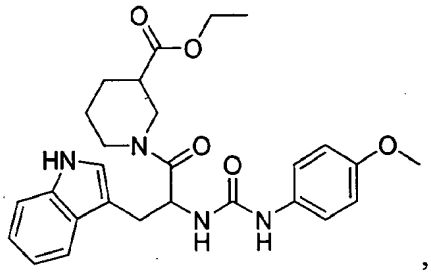
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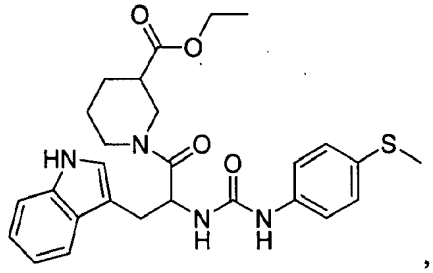
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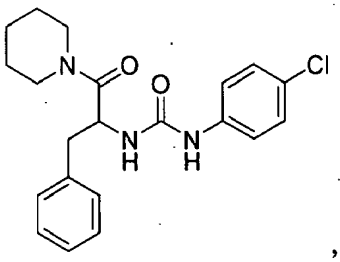
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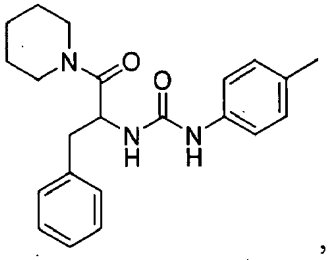
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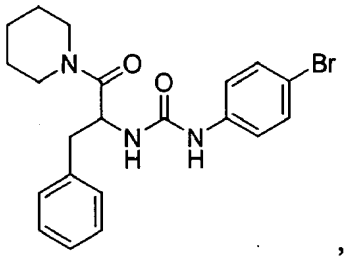
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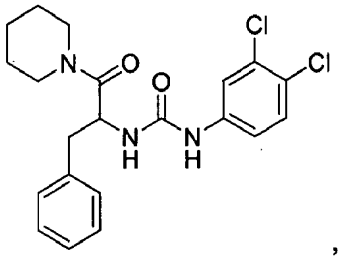
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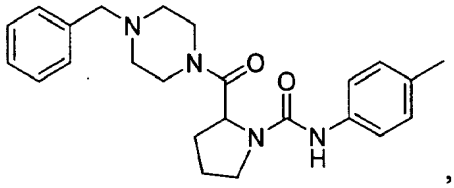
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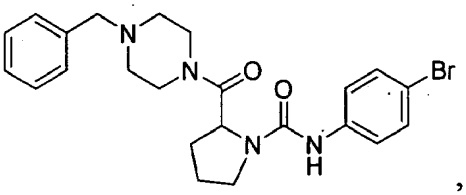
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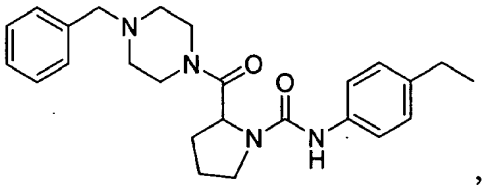
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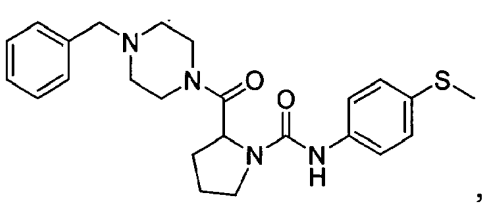
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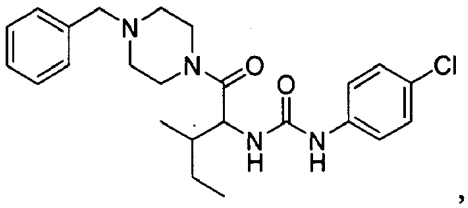
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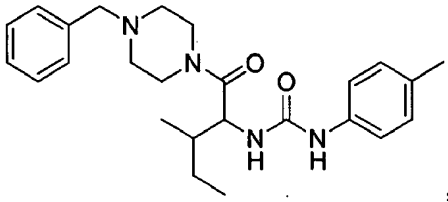
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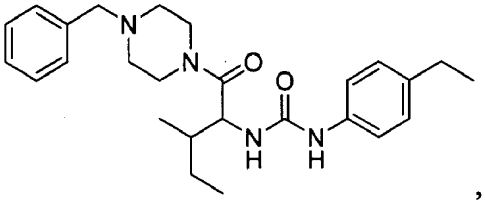
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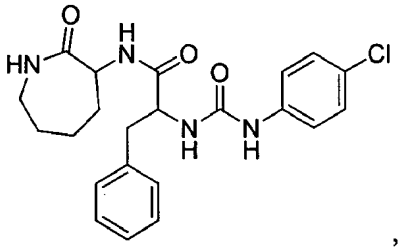
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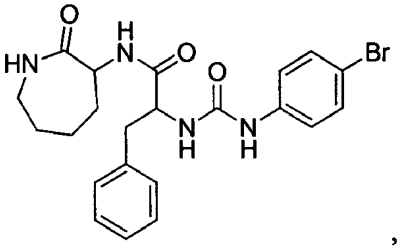
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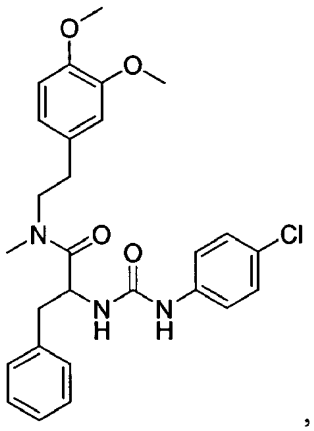
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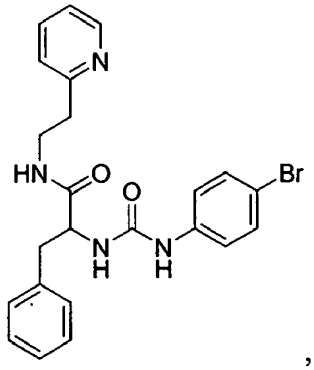
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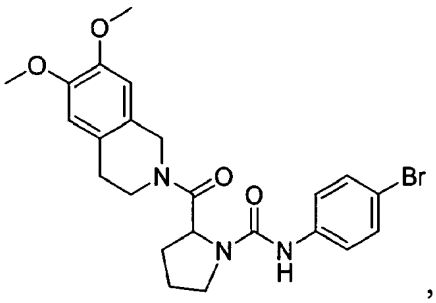
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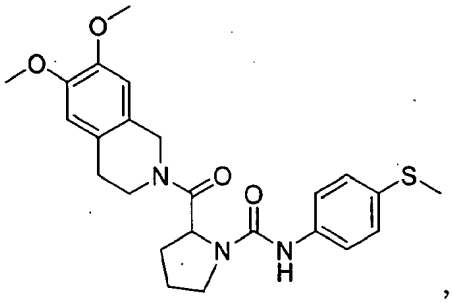
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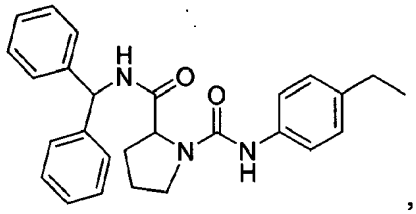
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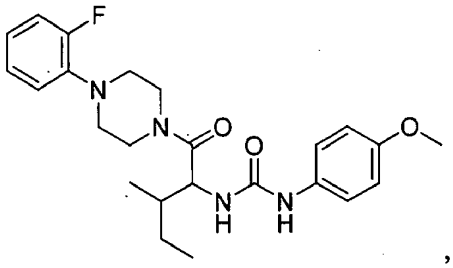
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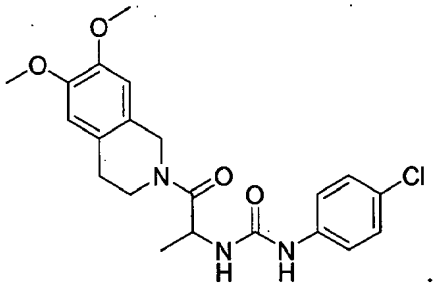
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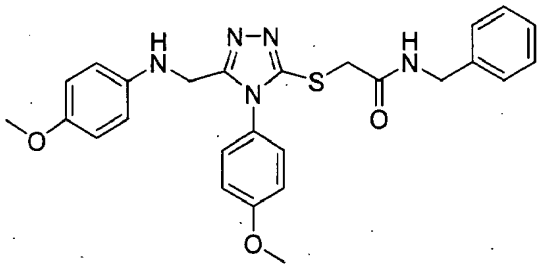
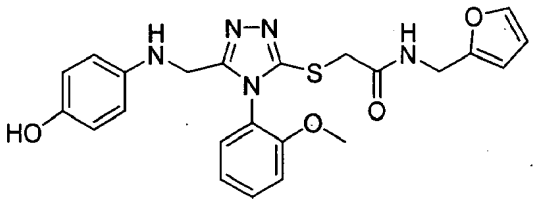
In certain embodiments, the methods are also directed to methods for treating acute and chronic inflammation. Particular preferred embodiments of compounds for use with the methods disclosed herein are represented by COMPOUNDS 1, 2, 3, 4, 5, and 6.


Compound 1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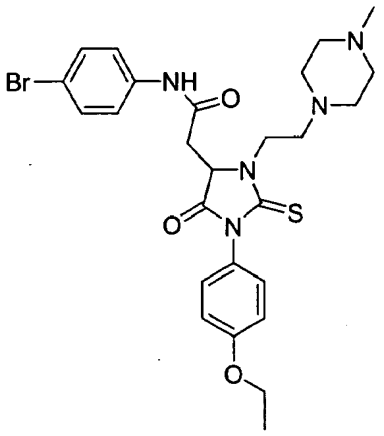

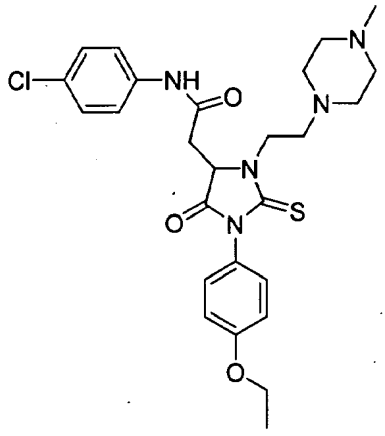

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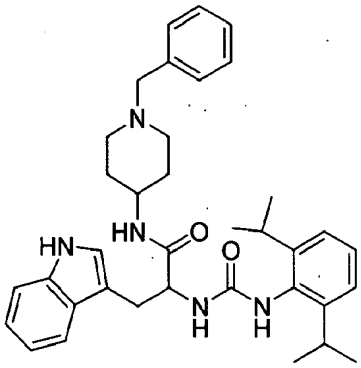
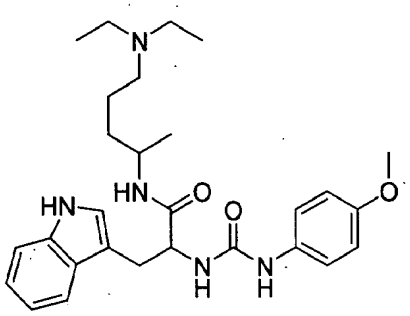


Compound 4



Compound 5

Compound 6

Certain of the compounds disclosed herein may exist as stereoisomers including optical isomers. The scope of the present disclosure includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

In another aspect, disclosed herein is a method for treating acute and chronic pain comprising identifying an individual in need thereof, and contacting said individual with an effective amount of at least one compound of Formula I, Formula II, or Formiula III as defined herein, whereby one or more symptoms of the pain are reduced.

Another aspect disclosed herein is the discovery that the disclosed FPRL1 compounds are specific agonists of the FPRL1 receptor. Therefore, these agonists are expected to bind to the FPRL1 receptor and induce anti-inflammatory responses. The agonists of FPRL1 receptor described herein can be used to treat acute or chronic inflammation.

Thus, in some embodiments, the compound of Formula I, Formula II, or Formula III activates the FPRL1 receptor. In certain embodiments, the compound may selectively activate the FPRL1 receptor subtype, but not the FPR or FPRL2 receptor.

[0172] The term "activate" refers to increasing the cellular function of the FPRL1 receptor. The receptor function is preferably the interaction with a natural binding partner. The term "natural binding partner" refers to a molecule that binds to a FPRL1 receptor in a cell.

In certain embodiments, the inflammation treated by the methods disclosed herein is associated with bacterial infection, viral infection, physical injury, including physical trauma and radiation exposure, vasoconstriction as a result of asthma, anaphylactic reactions, allergic reactions, shock, diabetes, rheumatoid arthritis, gout, psoriasis, allergic rhinitis, adult respiratory distress syndrome, Crohn's disease, endotoxin shock, traumatic shock, hemorrhagic shock, bowel ischemic shock, renal glomerular disease, benign prostatic hypertrophy, inflammatory bowel disease, myocardial ischemia, myocardial infarction, circulatory shock, brain injury including ischaemic stroke and hemorrhagic stroke, systemic lupus erythematosus, chronic renal disease, cardiovascular disease, and hypertension or chemical injury.

In another aspect, disclosed herein is a method of identifying a compound that alleviates inflammation in a subject, comprising identifying a subject suffering from inflammation; providing the subject with at least one compound of Formula I, Formula II, or Formula III, as defined herein; and determining if said at least one compound reduces inflammation in the subject.

In yet another aspect, disclosed herein is a method of identifying a compound of Formula I, Formula II, or Formula III which is an agonist of the FPRL1 receptor, the method comprising contacting a FPRL1 receptor with at least one compound of Formula I, Formula II, or Formula III, as defined herein; and determining any increase in activity level of the FPRL1 receptor so as to identify a compound of Formula I, Formula II, or Formula III , which is an agonist of the FPRL1 receptor.

In the context of present disclosure, an "agonist" is defined as a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor). An "antagonist" is defined as a compound, which blocks the action of an agonist on a receptor. A "partial agonist" is defined as an agonist that displays limited, or less than complete, activity such that it fails to activate a receptor *in vitro*, functioning as an antagonist *in vivo*.

The term "subject" refers to an animal, preferably a mammal, and most preferably a human, who is the object of treatment, observation or experiment. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans.

The term "therapeutically effective amount" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. This response may occur in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, and includes alleviation of the symptoms of the disease being treated.

In a further aspect, disclosed herein is a method of identifying a compound which is an agonist of a FPRL1 receptor, the method comprising culturing cells that express the FPRL1 receptor; incubating the cells with at least one compound of Formula I, Formula II, or Formula III as defined herein; and determining any increase in activity of the FPRL1 receptor so as to identify a compound of Formula I, Formula II, or Formula III which is an agonist of a FPRL1 receptor.

In another aspect, disclosed herein is a pharmaceutical composition comprising a compound of Formula I, Formula II, or Formula III as described above, and a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

The term "pharmaceutical composition" refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human

blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into the are of pain, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

Pharmaceutical compositions for use in accordance with the present disclosure thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations, which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

For injection, the agents disclosed herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds disclosed herein to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with pharmaceutical combination disclosed herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations, which can be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may

be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present disclosure are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents, which increase the solubility of the compounds to allow for the preparation of highly, concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds disclosed herein is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ , and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for de Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acids or base forms.

Pharmaceutical compositions suitable for use in the methods disclosed herein include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

The exact formulation, route of administration and dosage for the pharmaceutical compositions disclosed herein can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight, or 1 to 500 mg/kg, or 10 to 500 mg/kg, or 50 to 100 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. Note that for almost all of the specific compounds mentioned in the present disclosure, human dosages for treatment of at least some condition have been established. Thus, in most instances, the methods disclosed herein will use those same dosages, or dosages that are between about 0.1% and 500%, or between about 25% and 250%, or between 50% and 100% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an

adult human patient may be, for example, an oral dose of between 0.1 mg and 500 mg of each ingredient, preferably between 1 mg and 250 mg, e.g. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of each ingredient between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg of each ingredient of the pharmaceutical compositions disclosed herein or a pharmaceutically acceptable salt thereof calculated as the free base, the composition being administered 1 to 4 times per day. Alternatively the compositions disclosed herein may be administered by continuous intravenous infusion, preferably at a dose of each ingredient up to 400 mg per day. Thus, the total daily dosage by oral administration of each ingredient will typically be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will typically be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen, which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

The compositions may, if desired, be presented in a pack or dispenser device, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may

also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound disclosed herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

It will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure.

Example 1: Receptor Selection and Amplification Technology Assay

The functional receptor assay, Receptor Selection and Amplification Technology (R-SAT), was used to investigate the pharmacological properties of known and novel FPRL1 agonists. R-SAT is disclosed in U.S. Patent Nos. 5,707,798, 5,912,132, and 5,955,281, all of which are hereby incorporated herein by reference in their entirety, including any drawings.

Briefly, NIH3T3 cells were grown in 96 well tissue culture plates to 70-80% confluence. Cells were transfected for 16-20 h with plasmid DNAs using Polyfect (Qiagen Inc.) as per manufacturer's protocols. R-SATs were generally performed with 3 ng/well of receptor and 20 ng/well of β-galactosidase plasmid DNA. All receptor and G-protein constructs used were in the pSI-derived mammalian expression vector (Promega Inc) as described previously. The FPRL1 receptor gene was amplified by PCR from genomic DNA using oligodeoxynucleotide primers based on the published sequence (GenBank Accession # M84562). For large-scale transfections, cells were transfected for 16-20 h, then trypsinized and frozen in DMSO. Frozen cells were later thawed, plated at ~10,000 cells per well of a 96 half-area well plate that contained drug. With both methods, cells were then grown in a humidified atmosphere with 5% ambient CO_2 for five days. Media was then removed from the plates and marker gene activity was measured by the addition of the β-galactosidase

substrate *o*-nitrophenyl β-D-galactopyranoside (ONPG, in PBS with 0.5% NP-40). The resulting colorimetric reaction was measured in a spectrophotometric plate reader (Titertek Inc.) at 420 nm. All data were analyzed using the computer program XLFit (IDBSm). Efficacy is the percent maximal activation compared to activation by a control compound (WKYMVm in the case of FPRL1). pEC_{50} is the negative of the $\log(EC_{50})$, where EC_{50} is the calculated concentration in Molar that produces 50% maximal activation.

These experiments have provided a molecular profile, or fingerprint, for each of these agents at the human FPLR1 receptor. As can be seen in Table 1, these compounds selectively activate FPRL1 receptors relative to mock transfected cells.

TABLE 1

Compound	Generic Structure	pEC_{50}	%Efficacy
1	Formula I	5.9	90
2	Formula I	5.6	72
3	Formula II	5.8	112
4	Formula II	5.7	75
5	Formula III	5.6	98
6	Formula III	5.6	102

Efficacy is relative to the ligand WKYMVm.

Example 2: FPRL1 Receptor Binding Assay

Using the following reagents, supplies, and methods, the ability of the compounds disclosed herein to bind to the FPRL1 receptors can be readily determined in a receptor binding assay.

1. Grow FPRL1 receptor-transfected COS cells (or another transfected cell line that does not endogenously express the FPRL1 receptors may be substituted) in a suitable growth medium in 24-well culture plates.

2. Prepare radiolabeled assay solutions by mixing 245 µl of 0.25 nM [^{125}I]WKYMVm working solution with 5 µl of the following (one per solution): 50 µM unlabeled WKYMVm working solution, 0.25 nM [^{125}I] WKYMVm working solution, HEPES buffer only, or 50× test compound.

3. Aspirate medium from 24-well plates using a Pasteur pipet attached to a vacuum source. Do not wash cells.

4. Add 250 µl radiolabeled assay solution from step 2 to each assay well and incubate plates 60 min at room temperature (~22°C) on an orbital shaker at low speed.

5. Terminate the incubation by aspirating the radioactive solution with a 24-well Brandel cell harvester. Wash the wells three times with 0.5 ml ice-cold HEPES buffer using the cell harvester.

6. Aspirate the solution from the wells with a micropipettor and transfer to 12 × 75-mm polystyrene test tubes. Analyze with a gamma counter (Packard, Cobra II).

7. Determine specific binding and calculate the IC_{50} values.

Example 3: Determination of Changes in Cytosolic Calcium in Transfected HL-60 Cells

1. HL-60 cells transfected with FPRL1 or a control receptor at a density 1-3 x 10^6 cells/ml are washed with phosphate–buffered saline.

2. Cells are loaded with 2 µM Fura-2 and analyzed with respect to the rise in intracellular calcium in the presence or absence of varying concentration of compound.

3. The response is compared to that elicited by the application of the standard reference ligand WKYMVm when tested at 100nM.

Intracellular free calcium concentrations are calculated using the formula:

$$[Ca^{2+}]_i = \frac{K_d(F - F_{min})}{F_{max} - F}$$

where K_d for Fura-2 is 224 nM, F_{max} is the fluorescence in the presence of 0.04% Triton-X100 and F_{min} is the fluorescence obtained after the addition of 5 mM EGTA in 30 mM Tris-HCl, pH7.4.

Example 4: Sequences for FPRL1

SEQ ID NO:1, below, is the DNA sequence encoding the FPRL1 receptor. SEQ ID NO:2, below, is the polypeptide sequence for the FPRL1 receptor.

Sequence ID 1:

```
1 ggcacgagga acaacctatt tgcaaagttg gcgcaaacat tcctgcctga caggaccatg
```

```
  61 gacacaggtt gtagagatag agatggctct ggctgtgcat tcagcagatt ctgtagatag
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 361 gatagtttag atgaaaagag agcatgatat tttaagccct gagactggat aatatcacct
 421 atagaaagac tatatagaga taagagaggt ggggaacaag taaaagctgc gggacactcc
 481 taaatttaga gtcaaattta gagcagaaaa tactagcaaa ggggactgaa aagcggtggc
 541 caattgagct tcaaatgcaa gtgaaagtgt gttgtgtgta catttatcat ctcatggcac
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Sequence ID 2:

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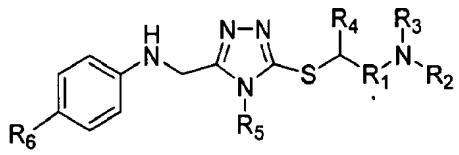
WHAT IS CLAIMED IS:

1. A compound of Formula I

(I) 

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

R_1 is selected from the group consisting of C_1-C_{10} straight chained or branched alkylene, oxygen, sulfur, NQ, CHCN, C=O, C=S, C=NQ, S=O, $S(=O)_2$, C=NOQ,

wherein Q is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl;

each of R_2, R_3, R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_2-C_{10} straight chained or branched alkenyl, C_2-C_{10} straight chained or branched alkynyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, -CN, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, and $-SR_7$,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched

alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl; or

R_3 and R_4 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring.

2. The compound of Claim 1, wherein R_1 is hydrogen or C_1-C_{10} straight chained alkyl.

3. The compound of Claim 2, wherein R_1 is C_1-C_5 straight chained alkyl.

4. The compound of Claim 1, wherein R_1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, and isopentyl.

5. The compound of Claim 1, wherein R_2 is selected from the group consisting of hydrogen, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is hydrogen or C_1-C_{10} straight chained alkyl.

6. The compound of Claim 5, wherein R_7 is hydrogen or C_1-C_3 straight chained alkyl.

7. The compound of Claim 1, wherein R_2 is selected from the group consisting of hydrogen, hydroxy, nitro, chloro, bromo, methoxy, and ethoxy.

8. The compound of Claim 1, wherein R_3 is selected from the group consisting of hydrogen, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is hydrogen or C_1-C_{10} straight chained alkyl.

9. The compound of Claim 8, wherein R_7 is hydrogen or C_1-C_3 straight chained alkyl.

10. The compound of Claim 1, wherein R_3 is selected from the group consisting of hydrogen, nitro, chloro, and iodo.

11. The compound of Claim 1, wherein R_4 is selected from the group consisting of hydrogen, C_1-C_{10} straight chained alkyl, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl.

12. The compound of Claim 1, wherein R_4 is selected from the group consisting of hydrogen, C_1-C_3 straight chained alkyl, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1-C_3 straight chained alkyl optionally substituted with an aryl.

13. The compound of Claim 1, wherein R_4 is selected from the group consisting of hydrogen, methyl, ethyl, hydroxy, nitro, amino, chloro, fluoro, methoxy, ethoxy, methylamino, dimethylamino, diethylamino, and benzyloxy.

14. The compound of Claim 1, wherein R_5 is selected from the group consisting of hydrogen, C_1-C_{10} straight chained alkyl, hydroxy, nitro, amino, halogen, perhaloalkyl, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl.

15. The compound of Claim 1, wherein R_5 is selected from the group consisting of hydrogen, C_1-C_3 straight chained alkyl, hydroxy, nitro, amino, halogen, perhaloalkyl, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1-C_3 straight chained alkyl.

16. The compound of Claim 1, wherein R_5 is selected from the group consisting of hydrogen, hydroxy, chloro, bromo, trifluoromethyl, and methoxy.

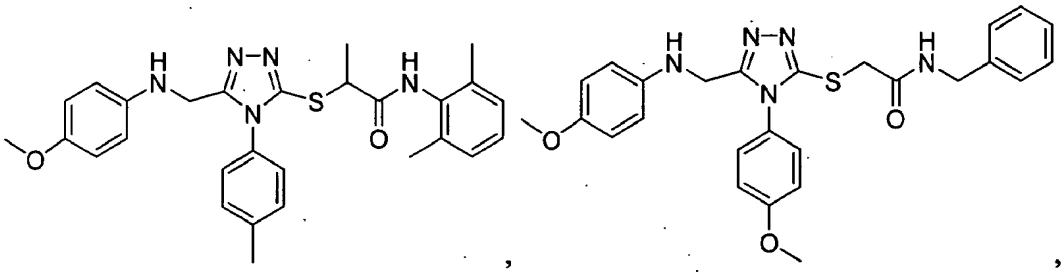
17. The compound of Claim 1, wherein R_6 is hydrogen.

18. The compound of Claim 1, wherein R_2 and R_3 and the nitrogen to which they are attached form a fused heteroaryl or heterocyclic alkyl ring.

19. The compound of Claim 18, wherein the ring is a heterocyclic alkyl ring.

20. The compound of Claim 19, wherein the heterocyclic alkyl ring is selected from the group consisting of N-morpholine and pyrrole.

21. A compound selected from the group consisting of



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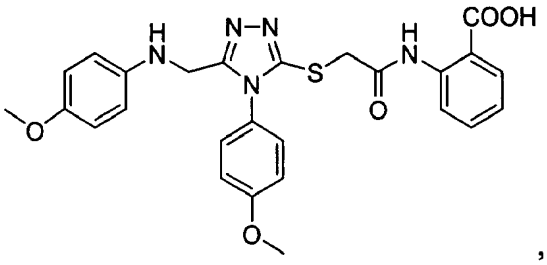
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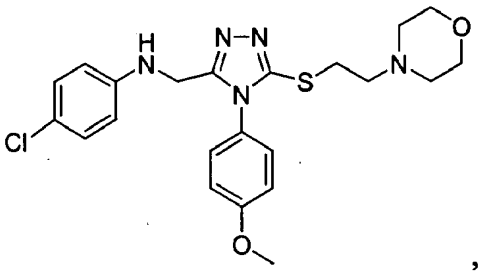
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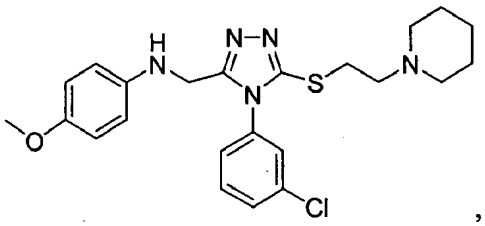
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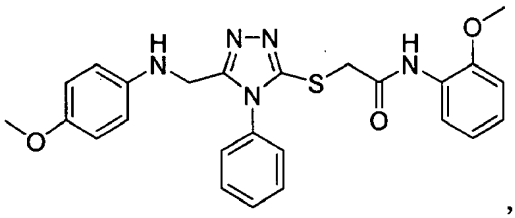
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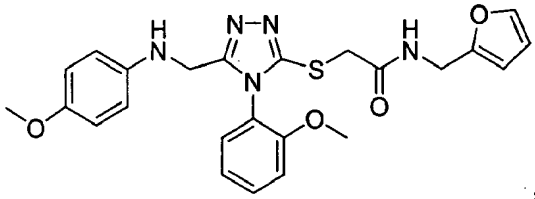
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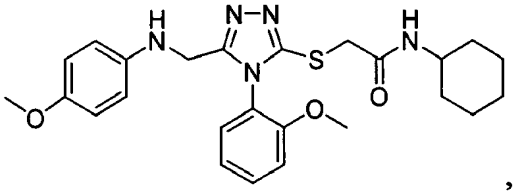
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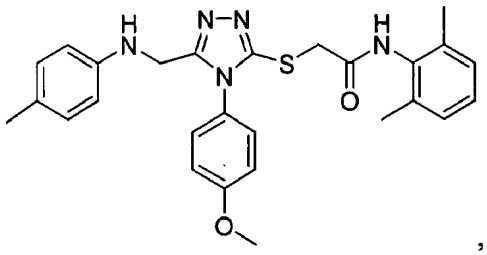
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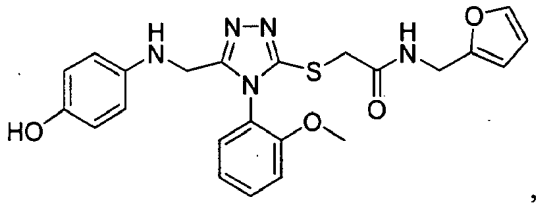
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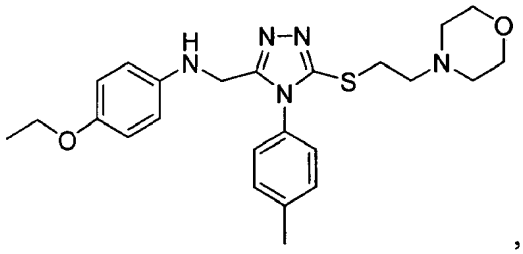
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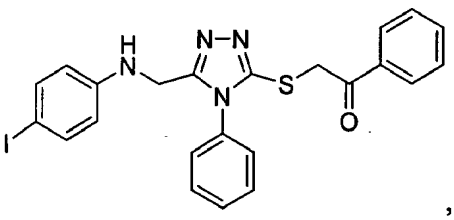
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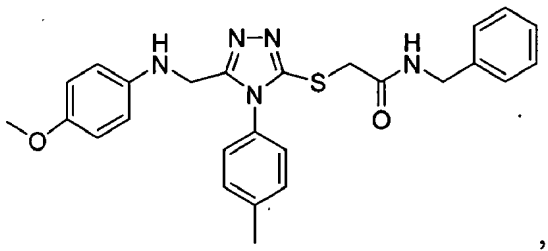
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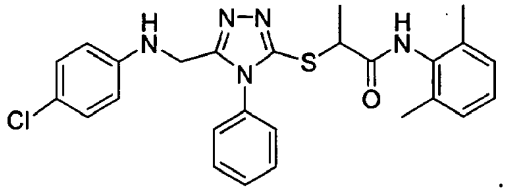
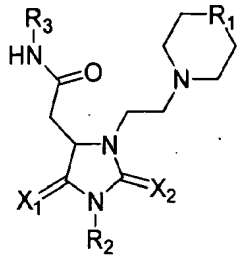


22. A compound of Formula II

(II) 

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

each of X_1 and X_2 is independently oxygen or sulfur;

R_1 is selected from the group consisting of C_1-C_{10} straight chained or branched alkylene, oxygen, sulfur, NQ, CHCN, C=O, C=S, C=NQ, S=O, $S(=O)_2$, C=NOQ

wherein Q is selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl;

each of R_2, R_3, is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_2-C_{10} straight chained or branched alkenyl, C_2-C_{10} straight chained or branched alkynyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, -CN, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, , and $-SR_7$,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched

alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl.

23. The compound of Claim 22, wherein R_1 is selected from the group consisting of oxygen and NQ, wherein Q is selected from the group consisting of hydrogen, C_1-C_5 straight chained or branched alkyl optionally substituted with an aryl or heteroaryl.

24. The compound of Claim 23, wherein Q is C_1-C_3 straight chained or branched alkyl.

25. The compound of Claim 23, wherein Q is selected from the group consisting of methyl, ethyl, and propyl.

26. The compound of Claim 23, wherein Q is methyl.

27. The compound of Claim 22, wherein R_2 is selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_3-C_{10} cycloalkyl, and optionally substituted aryl.

28. The compound of Claim 27, wherein R_2 is substituted aryl.

29. The compound of Claim 28, wherein R_2 is selected from the group consisting of 4-alkylphenyl, 4-alkoxyphenyl, 4-alkoxycarbonylphenyl.

30. The compound of Claim 28, wherein R_2 is selected from the group consisting of 4-methylpheynl, 4-ethoxyphenyl, and 4-ethoxycarbonylphenyl.

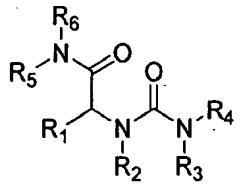
31. The compound of Claim 22, wherein R_3 is selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_3-C_{10} cycloalkyl, and optionally substituted aryl.

32. The compound of Claim 31, wherein R_3 is substituted aryl.

33. The compound of Claim 32, wherein R_3 is selected from the group consisting of 4-alkylphenyl, 4-alkoxyphenyl, and 4-halophenyl.

34. The compound of Claim 33, wherein R_3 is selected from the group consisting of 4-chlorophenyl, 4-bromophenyl, and 4-methoxyphenyl.

35. A compound of Formula III

(III) 

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

each of R_1, R_2, R_3, R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, C_1-C_{10} straight chained or branched alkyl, C_2-C_{10} straight chained or branched alkenyl, C_2-C_{10} straight chained or branched alkynyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, -CN, $-C(=Z)R_7$,$-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, , and $-SR_7$

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of C_1-C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2-C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3-C_{10} cycloalkyl, and C_5-C_{10} cycloalkenyl; or

R_3 and R_4 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring;

R_4 and R_5 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring; or

R_1 and R_2 and the nitrogen to which R_2 is attached form a fused heteroaryl, or heterocyclic ring.

36. The compound of Claim 35, wherein R_1 is selected from the group consisting of hydrogen and optionally substituted C_1-C_{10} straight chained or branched alkyl.

37. The compound of Claim 36, wherein R_1 is C_1-C_5 straight chained alkyl optionally substituted with an aryl or heteroaryl ring.

38. The compound of Claim 37, wherein said aryl ring is phenyl.

39. The compound of Claim 37, wherein said heteroaryl ring comprises nitrogen.

40. The compound of Claim 39, wherein said heteroaryl ring is indole.

41. The compound of Claim 36, wherein said R_1 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl.

42. The compound of Claim 36, wherein R_1 and R_2 and the nitrogen to which R_2 is attached form a fused heteroaryl, or heterocyclic ring.

43. The use of the FPRL1 receptor as a screening tool to identify compounds effective in treating inflammation.

44. A method of screening for a compound able to affect one or more activities of a FPRL1 receptor comprising the steps of,

a) contacting a recombinant cell with a test compound, wherein said recombinant cell comprises a recombinant nucleic acid expressing said FPRL1 receptor, provided that said cell does not have functional FPRL1 receptor expression from endogenous nucleic acid, and

b) determining the ability of said test compound to affect one or more activities of said FPRL1 receptor, and comparing said ability with the ability of said test compound to affect said one or more FPRL1 receptor activities in a cell not comprising said recombinant nucleic acid;

wherein said recombinant nucleic acid comprises a FPRL1 receptor nucleic acid selected from the group consisting of:

i) nucleic acid of SEQ ID NO 1,

ii) nucleic acid encoding the amino acid SEQ ID NO 2,

iii) a derivative of either nucleic acid molecule in i) or ii), wherein said derivative encodes a receptor having one or more activities of said FPRL1 receptor and comprises at least 20 contiguous nucleotides which can hybridize under stringent hybridization conditions

45. The method of claim 44, wherein said FPRL1 receptor nucleic acid encodes the amino acid sequence of a SEQ ID NO 2 derivative comprising at least 20 contiguous

nucleotides which can hybridize under stringent hybridizations conditions to a complement of at least 20 contiguous nucleotides encoding the amino acid sequence of SEQ ID NO 2.

46. A method for treating acute and chronic inflammation of any type comprising contacting an organism with an effective amount of at least one compound of Formula I, II, or III, wherein the compound activates a FPRL1 receptor subtype.

47. The method of claim 46 wherein the inflammation is associated with diabetes, viral infection, irritable bowel syndrome, amputation, cancer, bacterial infection, physical injury, including physical trauma and radiation exposure, vasoconstriction as a result of asthma, anaphylactic reactions, allergic reactions, shock, diabetes, rheumatoid arthritis, gout, psoriasis, allergic rhinitis, adult respiratory distress syndrome, Crohn's disease, endotoxin shock, traumatic shock, hemorrhagic shock, bowel ischemic shock, renal glomerular disease, benign prostatic hypertrophy, myocardial ischemia, myocardial infarction, circulatory shock, brain injury including ischaemic stroke and hemorrhagic stroke, systemic lupus erythematosus, chronic renal disease, cardiovascular disease, and hypertension or chemical injury.

48. A method of identifying a compound which is an agonist of the FPRL1 receptor, the method comprising:

contacting a FPRL1 receptor with at least one test compound of Formula I, II, or III; and

determining any increase in activity level of said FPRL1 receptor so as to identify a test compound which is an agonist of the FPRL1 receptor.

49. A method of identifying a compound which is an agonist of a FPRL1 receptor, the method comprising:

culturing cells that express said FPRL1 receptor;

incubating the cells or a component extracted from the cells with at least one test compound of Formula I, II, or III; and

determining any increase in activity of said FPRL1 receptor so as to identify a test compound which is an agonist of a FPRL1 receptor.

50. The method of claim 49, wherein the cultured cells overexpress said FPRL1 receptor.

51. The method of claim 49 or 50, wherein the identified agonist is selective for the FPRL1 receptor.

52. A method for treating inflammation comprising

contacting an individual suffering from inflammation with an effective amount of at least one compound of Formula I, II, or III,

whereby one or more symptoms of the inflammation is reduced.

53. The method of Claim 52 further comprising the step of identifying an individual in need of inflammatory treatment prior to the contacting step.

54. The method of Claim 52, wherein said compound of Formula I, II, or III selectively activates the FPRL1 receptor subtype.

55. A method for treating or preventing inflammation or an inflammatory response in the subject, comprising: administering to a subject an effective anti-inflammatory amount of a compound of claim 52.

56. A method of claim 52, wherein the inflammatory response results from the activation of leukocytes, which activation comprises leukocyte migration and generation of reactive oxygen species to evoke vascular leakage or edema.

57. A method of claim 53, wherein the inflammatory response is associated with rheumatoid arthritis, Azheimer's disease or asthma.

58. A method of claim 53, wherein the inflammatory response results from physical injury, including physical trauma and radiation exposure.

59. A method of inducing vasodilation to treat or prevent a vasocontractive response or condition, comprising: administering to a subject an effective vasodilatory amount of a compound of claim 10.

60. A method of claim 59, wherein the vasocontractive response or condition is selected from the group consisting of a renal hemodynamic disease, including glomerular disease, and a cardiovascular disease, including hypertension, myocardial infarction, and myocardial ischemia.

61. A method for antagonizing a vasoconstrictive response to a sulfidopeptide leukotriene in a subject, comprising: administering to the subject a composition of claim 10.

62. A method of claim 61, wherein the vasoconstrictive response to said leukotriene is associated with a medical disorder selected from the group consisting of: asthma, anaphylactic reactions, allergic reactions, shock, inflammation, rheumatoid arthritis, gout, psoriasis, allergic rhinitis, adult respiratory distress syndrome, Crohn's disease, endotoxin shock, traumatic shock, hemmorrhagic shock, bowel ischemic shock, renal glomerular disease, benign prostatic hypertrophy, inflammatory bowel disease, myocardial ischemia, myocardial infarction, circulatory shock, brain injury, systemic lupus erythematosus, chronic renal disease, cardiovascular disease, and hypertension.

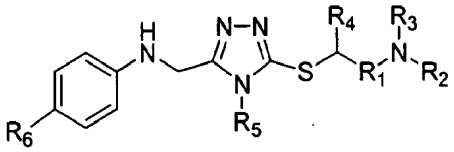
63. A method of claim 62, wherein the vasoconstrictive response is a renal vasoconstrictive response, including mild vasoconstriction, such as chronic renal disease, and chronic severe vasoconstriction, such as glomerular kidney disease.

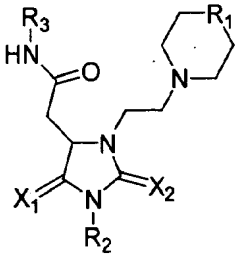
64. A method for stimulating cell proliferation in a subject to treat or prevent myeloid suppressive disorders comprising: administering to the subject an effective amount of the compound of claim 10.

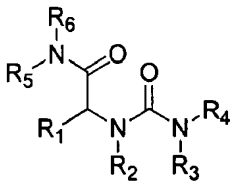
Identification of Compounds with Activity on Lipoxin Receptors

Abstract of the Disclosure

Disclosed herein are compounds of Formula I, Formula II, or Formula III

(I) 

(II) 

(III) 

as defined herein, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, that selectively activate the FPRL1 receptor. Further disclosed are methods of alleviating inflammatory responses by regulating key steps in leukocyte trafficking and preventing neutrophil-mediated tissue damage by administering to a subject a therapeutically effective amount of a compound of Formula I, Formula II, or Formula III. In addition, methods of modulating, or specifically agonizing, the FPRL1 receptor administering an effective amount of a compound of Formula I, Formula II, or Formula III are also disclosed.